



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: September 25, 1981

SUBJECT: Registration Standard: Methoprene

FROM: Ellen Sullivan, Pharmacologist
Toxicology Branch/HED (TS-769) *EMS*

TO: Lois Rossi, Project Manager
Special Pesticide Review Division (TS-791)

THRU: William Butler, Section Head
Toxicology Branch/HED (TS-769) *WMB*
William Burnam, Acting Chief
Toxicology Branch/HED (TS-769) *WB*

Attached are the Topical Discussions, Toxicology Profile, Toxicology Hazard Assessment and Data Requirement Tables for Methoprene.

Please note that toxicology data has been reviewed for technical methoprene containing 68-96% A.I. methoprene. This data has been considered adequate to evaluate the currently registered technical chemical containing 92.4% A.I. methoprene.

Attachment

cc
Ann Barton
Judy Heckman

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METHOPRENE
Registration Standard
Topical Discussions
and
Disciplinary Review

Prepared By: Eileen Sullivan
Pharmacologist

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Acute Testing

Acute Oral Toxicity 163.81-1

The minimum data requirement for testing acute oral toxicity (LD₅₀) is one test on the technical chemical and on each manufacturing use and formulated product, preferably using the laboratory rat. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

Technical

Adequate data were available to evaluate the acute oral toxicity of technical methoprene.

In a study, (Hallesy, et. al., 1972, MRID: 00024607) 5 male and 5 female Sprague-Dawley rats were given a single oral dose of 10 g/kg methoprene (68.9% A.I.). No deaths or clinical signs of toxicity were observed during the 21 day observation period. Body weight gain and food and water consumption were normal. At necropsy no treatment related gross pathological alterations were observed. The data indicate an acute oral LD₅₀ of greater than 10 g/kg methoprene, in rats.

In another study (Jorgenson and Sasmore, 1972, MRID: 00024613) 5 groups of 2 male Sprague-Dawley rats were given single oral doses of 10.2 to 51.9 g/kg methoprene (68.9% A.I.) 1 out of 2 rats at 51.9 g/kg died on the sixth day following treatment. No other mortalities were observed during the two week observation period. Gross pathological examination showed blood colored fluid in the stomach and urinary bladder of the rat that died during the study; no gross pathological changes were observed in the surviving animals. This study also supports an acute oral LD₅₀ of greater than 10 g/kg for technical methoprene, in rats.

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Data were also available to evaluate the acute oral toxicity of technical methoprene in dogs. Hallesy et. al., 1972 (MRID: 00024609) gave 2 male and 2 female Beagle dogs a single oral dose of 10 g/kg methoprene (68.9% A.I.) and observed signs of severe toxicity that included anger, dilated pupils, rapid respiration, ataxia, salivation, vomiting and convulsions. By 2 hours after treatment 3 dogs had died and the fourth dog was sacrificed at 3 hours because of severe toxicity. Gross pathological examination showed congestion of the kidneys, liver, lungs and scleral vessels and telangiectasis in the livers. The study was then repeated using lower doses of methoprene. In the second study, 3 groups of 1 male and 1 female Beagle dogs were given single oral doses of 1.0, 2.0 or 5.0 g/kg methoprene (68.9% A.I.) and no deaths or clinical signs of toxicity were observed during a 21 day observation period. Body weight gain and food and water consumption were normal. At necropsy no treatment related pathological changes were observed. Based on these findings, an LD₅₀ of greater than 5 g/kg but less than 10 g/kg methoprene is indicated in dogs.

The above data indicate a high, acute oral LD₅₀ for methoprene in rats and dogs. Based on these findings, technical methoprene should be placed in Toxicity Category IV for acute oral toxicity.

Manufacturing Use (M.U.)

No data were available to assess the acute oral toxicity of the M.U. formulations containing 10-80% methoprene.

Based on an evaluation of the inert ingredients, an acute oral toxicity test is required on the existing M.U. product containing 15% methoprene.

Emulsifiable Concentrates (E.C.)

Adequate data were available to assess the acute oral toxicity of an E.C. containing 65.9% A.I. methoprene. (Hepler et. al., 1979, MRID: 00010913) when 5 male and 5 female Wistar rats were given a single oral dose of 5 g/kg of an E.C. containing 65.9% A.I. methoprene no mortalities or clinical signs of toxicity were observed during a 14 day observation period. At necropsy, no treatment related gross pathological abnormalities were observed. The data indicate an acute oral LD₅₀ of greater than 5 g/kg for this product. Thus, this product should be placed in Toxicity Category IV for acute oral toxicity.

Adequate data were also available to evaluate the acute oral toxicity of an E.C. containing 10% A.I. methoprene. (Hallesy et. al., 1972, MRID: 00024609). In this study, no mortalities or clinical signs of toxicity were observed when 5 groups of 5 male and 5 female Sprague-Dawley rats were given single oral doses of 0.625 to 10 g/kg of an E.C. containing 10% A.I. methoprene. At necropsy, no treatment related gross pathological changes were observed. The data indicate an acute oral LD₅₀ of greater than 10 g/kg for this product. Based on these results this product should be placed in Toxicity Category IV for acute oral toxicity.

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No further acute oral toxicity testing is required with the existing E.C. products containing methoprene as their single active ingredient.

Granular (G) and Pelleted/Tableted (P/T)

No data were available to evaluate the acute oral toxicity of the G or P/T formulations containing 0.02 to 7.9% methoprene. Since the Confidential Statements of Formulation (CSF) do not indicate an anticipated change in the acute oral toxicity of these products, due to their inert ingredients, testing of the technical chemical is sufficient. Thus, these products should be placed in Toxicity Category IV for acute oral toxicity and additional testing in this discipline is not needed.

Pressurized Liquids (P.R.L.)

No data were available to assess the acute oral toxicity of the P.R.L. formulation containing 0.15% methoprene. Based on an evaluation of the inert ingredients, testing of the M.U. product containing 15% methoprene should be sufficient to fulfill this data requirement. Therefore, acute oral toxicity testing with this product is not required.

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Metabolites

ZR-724 Technical (11-hydroxy-3,7,11-trimethyl-dodeca-2,4-dienoic acid)

The acute oral LD₅₀ for ZR-724 technical in rats was determined to be greater than 6.81 g/kg. In a study (Johnston and Knott, 1972, MRID:) 4 groups of 5 male and 5 female Charles River CD rats were given a single oral dose of 2.15, 3.16, 4.64 or 6.81 g/kg ZR-724 in PEG 300 solution. One male and 2 females at 4.64 and 1 male at 6.81 died during the 14 day observation period. Other signs of toxicity included depression, observed at all dose levels, and salivation at the 2 highest doses. At necropsy, the male rat at 4.64 g/kg that died during the study showed weight loss and a bloated stomach. No other pathological observations were observed.

ZR-725 Technical (11-methoxy-3,7,11-trimethyl-dodeca-2,4-dienoic acid)

The acute oral LD₅₀ for ZR-725 technical was determined to be 4.87 g/kg (95% C.L. = 3.44-6.39 g/kg) in female rats and greater than 6.81 g/kg in male rats. In a study (Johnston and Knott, 1972, MRID:) 4 groups of 5 male and 5 female Charles River CD rats were given a single oral dose of 2.15, 3.16, 4.64 or 6.81 g/kg ZR-725. Signs of toxicity included death of some rats at the 3 highest doses; salivation; depression and convulsions at 4.64 and 6.81 g/kg.

At the lower doses only depression was observed. At necropsy, 1 male at 3.16 g/kg, that died during the study had a darkened liver and bloated stomach. In addition, 1 female at 4.64 g/kg, that died early, had an intestinal blockage. No other pathological alterations were observed.

These data indicate a low toxicity for 2 of the primary methoprene metabolites ZR-724 and ZR-725.

Acute Dermal Toxicity 163.81-2

The minimum data requirement for testing acute dermal toxicity (LD₅₀) is one test on the technical chemical and on the manufacturing use and formulated products, preferably using the albino rabbit. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

Technical

An acute dermal toxicity study in rabbits, using technical methoprene (68.9% A.I.), was conducted at Industrial Biotech Laboratories (IBT-1972). The toxicological evaluation of this study is pending receipt of the results from the audit validation program.

However, in an adequate study (Hepler et.al., 1979, MRID: 00010914), an emulsifiable concentrate (E.C.) formulation of methoprene (65.9% A.I.) did not produce mortality in rabbits given 24 hour dermal exposure to 2 g/kg of the product. (See specific details under E.C.'s).

The acute dermal LD₅₀ for this product was indicated as greater than 2 g/kg. The high dermal LD₅₀ observed here suggests a low potential for acute dermal toxicity with methoprene. Thus, this data is considered adequate to fulfill acute dermal toxicity testing requirements for technical methoprene and places it in Toxicity Category III for acute dermal toxicity.

Manufacturing Use (M.U.)

No data were available to assess the acute dermal toxicity of the M.U. formulations containing 10-80% methoprene.

Based on an evaluation of the inert ingredients, an acute dermal toxicity test is required on the existing M.U. product containing 15% methoprene.

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Emulsifiable Concentrates (E.C.)

Adequate data were available to assess the acute dermal toxicity of an E.C. containing 65.9% A.I. methoprene (Hepler et.al., 1979, MRID: 00010914). In this study, 4 male and 4 female New Zealand White rabbits were given 24 hour dermal exposure to 2 g/kg of an E.C. containing 65.9% A.I. methoprene. The test material was applied to the shaved, abraded and intact skin of the animals under an occlusive wrap. No deaths were observed; 2 out of 8 animals lost weight during this study however, this was attributed to a respiratory disorder and not to the chemical. No other clinical signs of toxicity were observed during a 14 day observation period. In addition, no edema or erythema were observed at the test site. However, the treated skin of all the rabbits was dry and stiff; scab formation (which was observed in all animals) sloughed off by 14 days and revealed healthy skin beneath. At necropsy, 3 out of 8 rabbits had respiratory congestion, this effect was not considered treatment related. The data indicate a dermal LD₅₀ of greater than 2 g/kg for this product. Based on these results, this product should be placed in Toxicity Category III for acute dermal toxicity.

Adequate data were also available to assess the acute dermal toxicity of an E.C. containing 10% A.I. methoprene (Olson, 1972, MRID: 00024618). In this study, 3 groups of 4 New Zealand White rabbits were given 24 hour dermal exposure to 1, 3 or 9 g/kg of an E.C. containing 10% A.I. methoprene. The test material was applied to the shaved, abraded or intact, skin of the rabbits under an occlusive rubber wrap. No mortalities were observed during the 14 day observation period. Slight or moderate erythema was observed at some test sites at 24 hours, it persisted, to a slight degree in some animals at 48 hours. Blanched skin was also observed at some abraded sites. In addition, slight skin desquamation was observed at abraded sites on days 2 through 4. Two rabbits at 3 g/kg and 1 rabbit at 9 g/kg had pale brown kidneys at necropsy. The dermal LD₅₀ of this product was determined to be greater than 9 g/kg. Thus, this product is placed in Toxicity Category III for acute dermal toxicity.

No further acute dermal toxicity testing is required with the existing E.C. products containing methoprene as their single active ingredient.

Granular (G) and Pelleted/Tableted (P/T)

No data were available to evaluate the acute dermal toxicity of the G or P/T formulations containing 0.02 to 7.9% methoprene. Since the CSF's do not indicate an anticipated change in the acute dermal toxicity of these products, due to their inert ingredients, testing of the technical chemical is sufficient. Thus, these products should be placed in Toxicity Category III for acute dermal toxicity and additional testing in this discipline is not needed.

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Pressurized Liquids (P.R.L.)

No data were available to assess the acute dermal toxicity of the P.R.L. formulation containing 0.15% methoprene. Based on an evaluation of the inert ingredients, testing of the M.U. product containing 15% methoprene should be sufficient to fulfill this data requirement. Therefore, acute dermal toxicity testing with this product is not required.

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Acute Inhalation Toxicity 163.51-3

Acute inhalation testing is required to support the registration of the manufacturing use product and formulated products if: the product is a gas, the product produces a respirable vapor or 20% or more of the aerodynamic equivalent of the product is composed of particles not larger than 10 microns. Testing in the laboratory rat is preferred.

The vapor pressure of technical methoprene (2.37×10^{-5} mm Hg at 25°C and 1.60×10^{-4} mm Hg at 40°C) indicates that it is likely to form a respirable vapor. In addition, emulsifiable concentrate formulations of methoprene are applied by methods (multidirectional sprayers and aerial application) that would permit inhalation exposure. Therefore, acute inhalation testing is required.

Technical

Adequate data were available to assess the acute inhalation toxicity of technical methoprene. When rats were exposed to 0, 2 or 20 mg/L (nominal concentration) of aerosolized methoprene (68.9% A.I.) for 4 hours a day, 5 days a week for 3 weeks (Olson and Willigan, 1972, MRID:) no treatment related mortalities, clinical signs of toxicity (other than nasal discharge at 20 mg/L) or pathological alterations were observed. (See specific details of this study under the Subchronic Inhalation Toxicity section of this report). From this data an acute inhalation LC₅₀ of greater than 20 mg/L is estimated. Thus, based on these results technical methoprene should be placed in Toxicity Category IV for acute inhalation toxicity.

Two inhalation studies in rats and guinea pigs (MRID: and MRID: , separately) were determined to be invalid since no information was available to verify the concentration of the test material that the animals were exposed to. (Specifically, the airflow rate and the amount of test material aerosolized were not reported.)

Manufacturing Use (M.U.)

No data were available to assess the acute inhalation toxicity of the M.U. formulations containing 10-80% methoprene.

Based on an evaluation of the inert ingredients, an acute inhalation toxicity test is required with the M.U. product containing 15% methoprene.

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Emulsifiable Concentrate (E.C.)

No data were available to assess the acute inhalation toxicity of the E.C. formulations containing 5-65.9% methoprene. Based on an evaluation of the inert ingredients and the available acute data that indicates a low toxicity potential for these products, acute inhalation toxicity testing is not required. These products should be placed in Toxicity Category IV for acute inhalation toxicity based on the results from testing of the technical chemical.

Granular (G) and Pelleted/Tableted (P/T)

No data were available to evaluate the acute inhalation toxicity of the G or P/T formulations containing 0.02 to 7.9% methoprene. Since the CSF's do not indicate an anticipated change in the acute inhalation toxicity of these products, due to their inert ingredients, testing of the technical chemical is sufficient. Thus, these products should be placed in Toxicity Category IV for acute inhalation toxicity and additional testing in this discipline is not needed.

Pressurized Liquids (P.R.L.)

No data were available to assess the acute inhalation toxicity of the P.R.L. formulation containing 0.15% methoprene. Based on an evaluation of the inert ingredients, testing of the M.U. product containing 15% methoprene should be sufficient. Therefore, acute inhalation toxicity testing with this product is not required.

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The Acute Toxicity of Methoprene by Intraperitoneal Injection

Data were available to evaluate the acute intraperitoneal (i.p.) toxicity of technical methoprene in rats. When 6 groups of male and female Sprague-Dawley rats (10-30 rats/group) were given single i.p. injections of 3.04 to 51.9 g/kg of technical methoprene (68.9% A.I.) the LD₅₀ was estimated as 4.8 g/kg (95% C.L. = 4.2-5.6 g/kg) (Jorgenson and Sasmore, 1972, MRID: 00024613). Clinical signs of toxicity observed, included depression, slight muscular tremors, lacrimation, diarrhea and abdominal distention. All survivors appeared normal by 6 to 10 days after treatment.

At necropsy, gross pathological alterations were mainly in the abdominal cavity and included fibrinous peritonitis (adhesions) and some hyperemic areas on the small intestines. In some instances, enlarged livers, kidneys and spleen were observed and thyroids were hemorrhagic or congested.

In a second experiment, these same authors, gave 20 male and 20 female Sprague-Dawley rats 3 g/kg methoprene (68.9% A.I.) intraperitoneally, for 2 days. (The second dose was given 24 or 48 hours following the first.) One male rat died 1 day after its second injection; no other mortalities were observed. No clinical signs of toxicity were observed during the two week observation period. At necropsy, all the animals showed moderate to severe fibrous peritonitis, yellow exudates in the abdominal cavity and slightly enlarged livers and spleens.

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Primary Eye Irritation 163.81-4

The minimum data requirement for primary eye irritation is one test on the manufacturing use and formulated products, preferably using the albino rabbit. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are not expected to add to the toxicity of the product.

In addition, a primary eye irritation data requirement may be waived if data is submitted demonstrating that the test substance has a pH of 1-3 or 12-14; for regulatory purposes, a test substance with a pH of 1-3 or 12-14 will be considered corrosive to the eye.

Technical

Adequate data were available to assess the primary eye irritation potential of technical methoprene. In a study (Hill and Hallesy, 1972, MRID: 00024614), no eye irritation or corneal opacity was observed in rabbit eyes at 24, 48 and 72 hours following instillation of 0.1 ml of methoprene (68.9%). In addition, no clinical signs of toxicity were observed during a 3 day observation period. The primary eye irritation score was zero out of possible 110 score. The test material is not a primary eye irritant; it should be placed in Toxicity Category IV for eye irritation.

Manufacturing Use

No data were available to evaluate the primary eye irritation potential of the M.U. formulations containing 10-80% methoprene.

Based on an evaluation of the inert ingredients, primary eye irritation testing with each existing product is required.

Emulsifiable Concentrate (E.C.)

Adequate data were available to assess the primary eye irritation potential of an E.C. containing 65.9% A.I. methoprene. (Hepler et.al., 1979, MRID: 00010915). In this study, slight conjunctival irritation was observed in washed and unwashed rabbit eyes up to 72 hours following the instillation of 0.1 ml of an E.C. containing 65.9% A.I. methoprene. By 7 days all of the treated eyes appeared normal. This product is not a primary eye irritant and should be placed in Toxicity Category III for eye irritation.

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Adequate data were also available to assess the primary eye irritation potential of an E.C. containing 10% A.I. methoprene. (Hallesy and Hill, 1972, MRID:). In this study, slight conjunctival irritation was observed in washed and unwashed rabbit eyes at 1 hour following the instillation of 0.1 ml of an E.C. containing 10% A.I. methoprene. The irritation cleared by 24 hours and the animals eyes remained normal during the remaining 7 day observation period. This product is not a primary eye irritant and should be placed in Toxicity Category III for eye irritation.

No data were available to assess the primary eye irritation potential of an E.C. containing 5% methoprene. Based on an evaluation of the inert ingredients in this product, primary eye irritation testing is required.

Granular (G) and Pelleted/Tableted (P/T)

No data were available to evaluate the primary eye irritation potential of the G or P/T formulations containing 0.02-7.9% methoprene. One eye irritation test is required with a granular formulation of methoprene. This test will satisfy the eye irritation testing requirements for the existing G and P/T products.

Pressurized Liquids (P.R. .)

No data were available to assess the primary eye irritation potential of the P.R.L. formulation containing 0.15% methoprene. Since this product contains a propellant, primary eye irritation testing is required.

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Primary Dermal Irritation 163.81-5

The minimum data requirement for primary dermal irritation is one test on the manufacturing use and formulated products, preferably using the albino rabbit. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

In addition, a primary dermal irritation data requirement may be waived if data is submitted demonstrating that the test substance has a pH of 1-3 or 12-14; for regulatory purposes, a test substance with a pH of 1-3 or 12-14 will be considered corrosive to the skin.

Technical

Adequate data were available to assess the primary dermal irritation potential of technical methoprene. In a study, female New Zealand albino rabbits were given 24 hour dermal exposure to 0.5 ml of methoprene (68.9% A.I.). (Hallesy and Hill, 1972, MRID: 00028615). The test material was applied to the shaved, abraded and unabraded, skin of each rabbit under an occlusive wrap. No dermal irritation was observed at 24 or 72 hours. The primary dermal irritation score was zero out of a possible 8 score. The test material is not a primary skin irritant, it should be placed in Toxicity Category IV for dermal irritation.

Manufacturing Use (M.U.)

No data were available to evaluate the primary dermal irritation potential of the M.U. formulations containing 10-80% methoprene.

Based on an evaluation of the inert ingredients, a primary dermal irritation test is required on the M.U. product containing 15% methoprene.

Emulsifiable Concentrates (E.C.)

In an adequate study (Hepler, et.al., 1979, MRID: 00010915), no edema or erythema were observed on the shaved, abraded and intact, skin of rabbits given 24 hour dermal exposure to 0.5 ml of an E.C. containing 65.9% A.I. methoprene. The primary dermal irritation score was 0 (out of a possible 8 score). At 5 days after treatment, some animals had cracking and flaking skin, by 2 weeks this condition had cleared. This product is not a primary skin irritant and should be placed in Toxicity Category IV for dermal irritation.

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In another adequate study (Hallesy and Hill, 1972, MRID:), the primary dermal irritation potential of an E.C. containing 10% A.I. methoprene was evaluated. In this study, female New Zealand albino rabbits were given 24 hour dermal exposure to 0.5 ml of an E.C. containing 10% A.I. methoprene. The test material was applied to the shaved, abraded and intact, skin of rabbits under an occlusive wrap. The primary dermal irritation score was 0 (out of a possible 8 score). This product is not a primary skin irritant, it should be placed in Toxicity Category IV for dermal irritation.

No further primary dermal irritation testing is required with the existing E.C. products containing methoprene as their single active ingredient.

Granular (G) and Pelleted/Tableted (P/T)

No data were available to evaluate the primary dermal irritation potential of the G or P/T formulations containing 0.02 to 7.9% methoprene. Since the CSF's do not indicate an anticipated change in the primary dermal irritation potential of these products, due to their inert ingredients, testing of the technical chemical is sufficient. Thus, these products should be placed in Toxicity Category IV for primary dermal irritation and additional testing in this discipline is not needed.

Pressurized Liquid (P.R.L.)

No data were available to assess the primary dermal irritation potential of the P.R.L. containing 0.15% methoprene. Based on an evaluation of the inert ingredients, testing of the M.U. product containing 15% methoprene should be sufficient to fulfill this data requirement. Therefore, primary dermal irritation testing is not required with this product.

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Dermal Sensitization 163.81-6

The minimum data requirement for dermal sensitization is an intradermal test on the manufacturing use and formulated products, preferably using the guinea pig. Separate testing is not required on a formulated product if adequate testing has been done on a similar product whose inert ingredients are expected to produce similar toxicity or if the inert ingredients are not expected to add to the toxicity of the product.

Technical

No data were available to evaluate the dermal sensitization potential of technical methoprene. However, the available acute data and the chemical structure of methoprene do not indicate a need for this type of test. Therefore, this testing requirement is waived.

Manufacturing Use (M.U.)

No data were available to evaluate the dermal sensitization potential of the M.U. formulations containing 10-80% methoprene.

Based on an evaluation of the inert ingredients, testing of the dermal sensitization potential of the M.U. product containing 15% methoprene is required.

Emulsifiable Concentrates (E.C.)

No data were available to assess the dermal sensitization potential of the E.C. formulations containing 5-65.9% methoprene. Based on an evaluation of the inert ingredients in these products and the available acute data, testing is not needed.

Granular (G) and Pelleted/Tableted (P/T)

No data were available to evaluate the dermal sensitization potential of the G or P/T formulations containing 0.02 to 7.9% methoprene. Based on an evaluation of the inert ingredients in these products and the available acute data on methoprene, testing is not needed.

Pressurized Liquid (P.R.L.)

No data were available to assess the dermal sensitization potential of the P.R.L. containing 0.15% methoprene. Based on an evaluation of the inert ingredients, testing of the M.U. product containing 15% methoprene should be sufficient to fulfill this requirement. Therefore, dermal sensitization testing with this product is not required.

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Acute Delayed Neurotoxicity 163.81-7

The minimum data requirement for acute delayed neurotoxicity is one test on the technical chemical, using the adult hen.

An acute delayed neurotoxicity test is required if the active ingredient, or any of its metabolites, degradation products, or impurities cause esterase depression or are structurally related to a substance that induces delayed neurotoxicity. There is no indication that suggests that methoprene or its metabolites cause esterase depression or are structurally related to known neurotoxins, therefore, acute delayed neurotoxicity testing is not required.

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Subchronic Testing

Subchronic Oral Toxicity 163.82-1

The minimum data requirements for subchronic oral toxicity is one test on the technical chemical in two mammalian species, preferably using the rat and dog.

A subchronic oral toxicity test is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation or is likely to result in repeated human exposure through the oral route. Tolerances and exemption from tolerances exist for methoprene; therefore, subchronic oral toxicity testing is required.

In a range finding study (Jorgenson and Sasmore, 1972, MRID: 00024610), 6 groups of 5 male and 5 female Sprague-Dawley rats were given 0, 1000, 5000, 10,000, 20,000 or 40,000 ppm methoprene (68.9% A.I.) in the diet for 2 weeks. Food consumption and body weight gain were markedly depressed at the 2 highest doses. These effects were attributed to palatability problems with the test material. After treatment with methoprene was discontinued in the third week, food consumption at 20,000 and 40,000 ppm returned to normal. Except for food rejection at the 2 highest doses, with resulting weight loss, no other clinical signs of toxicity were reported. At necropsy, gross pathological examination of the rats at the 40,000 dose level revealed no abnormalities. An effect level could not be established from this data because of palatability problems with the test material.

In another range finding study, these same authors (Jorgenson and Sasmore, 1972, MRID: 00024610) fed 5 groups of 3 male Beagle dogs 0, 1000, 5000, 10,000 or 20,000 ppm methoprene (68.9% A.I.) in the diet for 2 weeks. A dose related reduction in body weight gain which included weight loss at the 2 highest doses was observed. Food consumption was depressed in animals at 10,000 and 20,000 ppm during the treatment period. However, when methoprene treatment was discontinued during the third week of testing, food consumption in these animals returned to normal. At necropsy a dose related increase in liver weights was observed. Dogs at 10,000 and 20,000 ppm also displayed morphological changes in the liver, however, these changes were not described. The data indicate that the dog is less tolerant of high doses of methoprene than the rat. Based on the body weight and food consumption data, 5000 ppm is an estimated maximum tolerated dose (MTD) for a subchronic feeding study with dogs.

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In a 90 day feeding study (Jorgenson and Sasmore, 1972, MRID: 00024612) 15 male and 15 female Sprague-Dawley rats were fed diets containing 0, 250, 500, 1000 or 5000 ppm methoprene (68.9% A.I.). A significant increase in liver weights was observed in both males and females at the highest dose. In addition, kidney weights in males at 5000 ppm were significantly increased. Renal tubular regeneration was observed in 7 out of 15 males at 5000 ppm and 3 out of 15 males at 1000 ppm. The type of lesion associated with this effect was not described, however, its incidence suggests that it was treatment related. Based on these findings a no effect level (NEL) of 500 ppm is established. Further subchronic oral toxicity testing in rats is not required.

The NEL from a 90 day feeding study with methoprene in dogs was determined to be 500 ppm (Jorgenson and Sasmore, 1972, MRID: 00024612). In this study, 4 male and 4 female Beagle dogs were fed diets containing 0, 250, 500 or 5000 ppm methoprene (68.9% A.I.) for 90 days. The results showed that liver weights for males and females at 5000 ppm were significantly elevated. In addition, serum alkaline phosphatase (SAP) levels in males at 5000 ppm were elevated at the 4, 8 and 13 week testing intervals. Females at this dose had elevated SAP levels at the 8 week interval only. No other treatment related effects were observed. Taking into consideration the feed conversion factor, the NEL for dogs is lower (12.5 mg/kg) than for rats (25 mg/kg). Since this suggests that the dog is more sensitive to the toxic effects of methoprene than the rat, additional subchronic feeding, of a longer duration, is needed with the dog.

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21-Day Dermal Toxicity 163.82-2

The minimum data requirement for subchronic 21-day dermal toxicity is one study on the technical chemical, preferably using the albino rabbit.

A subchronic 21-day dermal toxicity test is required if pesticidal use is likely to result in repeated human skin contact.

Emulsifiable concentrate or pressurized liquid formulations of methoprene are used as sprays to control mosquito larva, tobacco beetles and moths, fleas and sciarid flies. These uses could result in repeated human skin exposure; therefore, 21-day dermal toxicity testing is required.

A 21-day dermal toxicity study in rabbits using methoprene (68.9% A.I.) was conducted at Industrial Biotest Laboratories (1972). The toxicological evaluation of this study is pending receipt of the results from the audit validation program.

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Subchronic 90-Day Dermal Toxicity 163.82-3

The minimum data requirement for subchronic 90-day dermal toxicity is one test for the technical chemical, preferably using the albino rabbit.

The subchronic 90-day dermal toxicity test is required if pesticidal use will involve purposeful application to the skin or will result in human exposure comparable to that, for example, from swimming pool additives or pesticide-impregnated fabrics. Methoprene is not used in the ways described above therefore, 90-day dermal toxicity testing is not required.

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Subchronic Inhalation Toxicity 163.82-4

The minimum data requirement for subchronic inhalation toxicity is one test on the technical chemical, preferably using the laboratory rat.

A subchronic inhalation toxicity test is required if pesticidal use may result in repeated inhalation exposure at a concentration that is likely to be toxic, as determined from results of an acute inhalation testing.

In a 21-day inhalation study (Olson and Willigan, 1972, MRID:), 3 groups of 10 male and 10 female albino rats were given repeated inhalation exposure to a nominal concentration of 0, 2, or 20 mg/L of aerosolized methoprene (68.9% A.I.). The animals were exposed to the test material 4 hours a day, 5 days a week, for 3 weeks. No treatment related mortalities were observed during the study. Rats exposed to 20 mg/L of the test material had nasal discharge during the exposure period; no other clinical signs of toxicity were observed. Body weight gain was comparable among the different groups and clinical biochemistry and hematology parameters did not indicate a consistent pattern of toxicity. In addition, lung, liver and kidney did not show compound related alterations. A NEL of 20 mg/L (HDT - highest dose tested) is established from this data.

Since emulsifiable concentrate (E.C.) formulations of methoprene are used to protect cigarette tobacco from damage by tobacco beetles and moths a special 6 week inhalation study in rats was conducted using cigarettes treated with the 5% E.C. formulation of methoprene.

In this study (Coate, 1978, MRID: 00010464) 3 groups of 10 male and 10 female Sprague-Dawley rats were given inhalation exposure to cigarette smoke from tobacco treated with 5% E.C. methoprene. The rats were exposed to the smoke 4 hours a day, 5 days a week for six weeks. Methoprene exposure was estimated as 0, 1.92 or 9.6 ug/kg/day. No compound related mortalities were observed. During exposure to the smoke the rats in all three groups were observed squinting. Some animals in the control group and highest dosed group were observed coughing during one exposure session. No other abnormalities in behavior or appearance were observed during the study. At necropsy, no compound related gross or histopathological alterations were observed. In addition, exposure to methoprene (5% E.C.) did not have a significant effect on body weight gain, clinical chemistry or hematological parameters and organ weights.

No additional subchronic inhalation testing is required with methoprene.

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Subchronic Neurotoxicity 163.82-5

The minimum data requirement for subchronic neurotoxicity testing is one test for the technical chemical, using either the adult hen or a mammalian species.

A subchronic neurotoxicity test is required if the pesticide has shown positive results in the acute delayed neurotoxicity test or induced irreversible neurological toxicity in mammalian species.

There is no evidence to suggest that methoprene is neurotoxic. Testing is not required.

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Chronic Testing

Chronic Feeding 163.83-1

A chronic feeding study is required if pesticidal use requires a tolerance or exemption from a tolerance, requires an issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the lifespan. Tolerances and exemption from tolerances exist for methoprene; therefore, a chronic feeding study is required.

In an adequate study, (Wazeter and Goldenthal, 1976, MRID: 00010739) 4 groups of 50 male and 50 female Charles River CD rats were fed diets containing 0, 250, 1000 or 5000 ppm methoprene (86.9% A.I.) for two years. No treatment related effects on body weight, food consumption, behavior, hematology, blood chemistry, urinalysis and organ weights were observed. Ophthalmoscopic examinations did not indicate a treatment related effect. At the end of the study, survival was approximately 50% in all groups. At necropsy no treatment related gross pathological or histopathological lesions were observed. In addition, there was no indication of an oncogenic effect since the incidence of tumors and types of tumors were observed with a similar frequency in control and treated animals. The no-effect-level (NEL) from this study is indicated as 5000 ppm (HDT). This data is adequate to fulfill chronic feeding testing requirements for methoprene. Further chronic feeding testing is not needed.

It should be noted, that a NEL of 500 ppm was established from an adequate 90-day rat feeding study (See Subchronic Feeding). The findings from the subchronic study suggest that younger rats are more susceptible to methoprene toxicity, while the chronic data indicates that older rats are more tolerant of the chemical. It appears from these studies that methoprene induced toxicological changes that occur early on in a rat's life are regenerative.

Oncogenicity 163.83-2

The minimum data requirement for oncogenicity, is testing in two mammalian species, preferably the rat and mouse, using the technical chemical.

An oncogenicity test is required if the active ingredient, or any of its metabolites, degradation products or impurities, is structurally related to a recognized carcinogen or causes a mutagenic effect, requires a tolerance or an exemption from a tolerance, requires an issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the lifespan. Tolerances and exemption from tolerances exist for methoprene; therefore, oncogenicity testing is required.

In an adequate study (Wazeter and Goldenthal, 1975, MRID: 00010739), 4 groups of 50 male and 50 female Charles River CD rats were fed diets containing 0, 250, 1000 or 5000 ppm methoprene (86.9%) for 2 years. (See specific details of this study under Chronic Feeding). No indication of an oncogenic effect was observed even at the highest dose level, 5000 ppm. The NEL for oncogenicity in rats is considered to be 5000 ppm (HDT).

The oncogenic potential of methoprene was also adequately evaluated in a 18 month study in mice (Wazeter and Goldenthal, 1975, MRID: 00010600).

In this study, 4 groups of 50 male and 50 female Charles River CD-1 mice were fed diets containing 0, 250, 1000 or 2500 ppm methoprene (86.9-87.5%) for 18 months. No difference was observed between the tumor incidence of mice in the control and treated groups. No treatment related effects on body weight, food consumption and general behavior were observed. At 18 months, survival was approximately 50% in all groups. At necropsy no treatment related gross pathological changes were observed. However, histopathological examination indicated a high incidence of brown pigmentation in mice at 2500 ppm. This finding was also observed in some mice at 1000 ppm but was absent at the 250 ppm level and in the control group. In addition, a higher incidence of liver focal necrosis was observed in 5000 ppm dosed females than in control ones. This difference was not observed in male mice. Amyloidosis was observed in various tissues at all dose levels including the control group; the incidence of this finding was approximately twice as great in high dosed animals compared to control ones.

The only parameters investigated in this study were body weight gain, food consumption, general behavior, gross and histopathology. Under these conditions, the NEL for systemic toxicity was indicated as 250 ppm (based on microscopic changes in the liver at the 2 highest doses). However, the NEL for oncogenicity is considered to be 2500 ppm.

The above data are adequate to fulfill oncogenicity testing requirements for methoprene. Further oncogenicity testing is not required.

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Reproductive Testing

Teratogenicity 163.83-3

The minimum data requirement for teratogenicity is testing in two mammalian species using the technical chemical.

Teratogenicity testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires an issuance of a food additive regulation, or is likely to result in a significant exposure to females. Tolerances and exemption from tolerances exist for methoprene; therefore, teratogenicity testing is required.

Adequate data were available to assess the teratogenic potential of Methoprene in rabbits (Nomura Research Institute, 1975, MRID:).

In this study, 4 groups of 10 pregnant rabbits were given 0, 50, 200 or 2000 mg/kg methoprene (95.7% A.I.) in olive oil, orally, on days 7 through 18 of gestation. No teratological effects were observed, however, maternal toxicity, as demonstrated by a 38.4% reduction in body weight gain and a 20% incidence of abortion, and fetotoxicity, indicated by an increase in embryo lethality, were observed at 2000 mg/kg/day. The study indicates a no effect level (NEL) of 200 mg/kg/day. Based on the doses tested, the lowest effect level (LEL) for maternal toxicity and embryolethality in utero was 2000 mg/kg/day. This study fulfills teratology testing requirements in one mammalian species.

In another teratology study (Nomura Research Institute, 1975, MRID:), 4 groups of at least 30 pregnant mice were given 0, 50, 200 or 600 mg/kg/day methoprene (95.7% A.I.) in olive oil, orally, on days 7 through 14 of gestation. On day 18 of pregnancy 20-23 mice in each group were sacrificed. Caesarians were performed and the effects on the fetuses were assessed. The remaining pregnant mice were allowed to whelp naturally and rear their litters for 3 or 7 weeks.

No maternal toxicity, fetotoxicity or teratogenicity were observed at the doses tested. However, the authors did not indicate the methods used to assess soft tissue anomalies. During the postnatal development, descent of the testes was retarded at 200 mg/kg and opening of the vagina was retarded at 50 mg/kg. In addition, testicular weight was significantly reduced at both these dose

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levels and one pup at 50 mg/kg had atrophied seminiferous tubules. Since these effects were not observed at the highest dose level, the toxicological significance of them is difficult to assess. The registrant has been asked to submit more information, including individual animal data, to address these issues. In addition, the registrant should indicate what procedures were used to assess fetuses for soft tissue anomalies. This study cannot be considered to fulfill teratology testing requirements, for methoprene, in a second mammalian species until the additional information requested is received and reviewed by the Agency.

Teratology studies in rats and rabbits using methoprene (68.9% A.I.) were conducted at Industrial Biotech Laboratories (1972). The toxicological evaluation of these studies is pending the receipt of the results from the audit validation program.

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Reproduction 163.83-4

The minimum data requirement for reproduction is testing in one mammalian species, preferably the laboratory rat, using the technical chemical and lasting two generations.

Reproduction testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires an issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the lifespan. Tolerances and exemption from tolerances exist for methoprene therefore, reproduction testing is required.

Adequate data were available to assess the reproductive toxicity of methoprene in rats (Killen and Rapp, 1974, MRID: 00010571). In a three generation reproduction study, 3 groups of male and female Long Evan rats were fed diets containing 0, 500 or 2500 ppm methoprene (86.9-87.5% A.I.). No compound related effects on body weight, food consumption, mating, fertility, gestation, litter size, viability and lactation were observed. Gross pathological examination of F3 offspring did not indicate compound related toxicity. The no effect level (NEL) for this study is 2500 ppm; the highest dose tested (HDT). Further reproduction toxicity testing with methoprene is not required.

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Mutagenicity 163.84-1 through 4

The following studies represent only the minimum requirements for data on the potential heritable effects of the technical material.

1. A mammalian in vitro point mutation test.
2. A sensitive submammalian point mutation test (bacteria, fungi or insects).
3. A primary DNA damage test (i.e., sister chromatid exchange or unscheduled DNA synthesis).
4. A mammalian in vivo cytogenetics test. If this test suggests a positive result, a dominant lethal or heritable translocation test may be required.

After results from these test systems and other Toxicology disciplines have been considered, additional testing may be required to further characterize or quantify the potential genetic risks.

Bacterial assays were conducted with methoprene. In a study (Hsia et.al., 1979, MRID: 05018270) methoprene (% A.I. unspecified) dissolved in dimethylsulfoxide (DMSO), at concentrations of 0.2, 2 and 20 ug/plate was evaluated for mutagenicity in Salmonella typhimurium strains TA-98, TA-100, TA-1535, TA-1537 and TA-1538.

The assays were run in the presence but not in the absence of metabolic activation. (The strains of bacteria used, detect base pair substitutions or frameshift mutagens). No evidence of mutagenicity was observed; however, the sensitivity of the assay cannot be adequately evaluated since no data were available for the positive controls and only a small range of low doses was evaluated.

In a dominant lethal study (Johnston 1973, MRID: 00010545) methoprene (68.9% A.I.) was given intraperitoneally (i.p.) to male rats at 20, 200 or 2000 mg/kg (the 2 lowest doses were diluted with PEG 300) as a single or repeated dose (2 or 5 daily doses). Negative controls received saline at 1 ml/kg and positive controls received triethylenemelamine (TEM) at 0.03 or 0.4 mg/kg. Rats were mated for 8 weeks. No effects indicative of powerful dominant lethality were observed with methoprene. The positive control caused a reduced number of implants and live fetuses per pregnancy and an increased number of resorptions, particularly during the first 5 weeks. This study does not provide a sensitive indication of the dominant lethal potential of methoprene since, the number of animals evaluated at each treatment regimen was small (5 males and 10 females) and there was a low proportion matings resulting in pregnancy (even in the negative control group).

Although the above data do not satisfy the Agency's mutagenicity testing requirements, they do suggest a lack of genetic toxicity with methoprene. Since a mutagenic effect is not anticipated, this data requirement can be waived at this time. However, the Agency reserves the right to ask for additional mutagenicity testing if a need is indicated in the future.

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Metabolism 163.8 -1

The minimum data requirement for metabolism is testing with a single dose of the analytically pure grade of the active ingredient in the radioactively labelled form.

A general metabolism study is required if a chronic feeding or oncogenicity study is required. Both these studies are required with methoprene since tolerances and exemption from tolerances exist.

The metabolism of methoprene has been investigated in the rat, mouse, guinea pig, cow and steer. Experimental data has shown that methoprene is extensively metabolized in each of these mammalian species; in addition, the data provide evidence that methoprene metabolites are incorporated into natural body constituents.

In a series of experiments (Chasseaud et al., 1974, MRID: 00010866 and Hawkins et al., 1977, MRID: 05007755) the excretion retention balance, biliary excretion, plasma kinetics and tissue distribution of radiolabelled methoprene and its metabolites were investigated in rats. 25 Ash Wistar rats of both sexes, were given single oral doses of 5-¹⁴C-methoprene (98% A.I.) in 70% ethanol. In 8 rats, the radioactivity of urine, feces and expired CO₂ was measured for 5 days. At the end of this period, the amount of radioactivity remaining in the bodies was determined. It was observed that 13% of the administered radiolabel was excreted in the urine in 24 hours and the value was increased to 19.6% by 5 days. 11.9% of the radiolabel was excreted in the feces after 48 hours increasing to 18.6% after 5 days. Expired air accounted for 25.5% of the radiolabel at 24 hours and 38.8% of it at 5 days. Tissue retention of the radiolabel accounted for 17.2% of it. From these data, the maximum excretion half life for about 60% of the radiolabel was estimated as about 10 hours and about 107 hours for an additional 15%.

In this same study, when 3 rats with cannulated bile ducts were given radiolabelled methoprene, an average of 27.4% of the label was recovered in the bile in 48 hours. This data was used to estimate the gastrointestinal absorption of methoprene which was indicated as 74% of the administered oral dose.

In the plasma kinetic portion of the experiment, blood samples were taken from the tail veins of 6 rats for up to 5 days following dosing with 5-¹⁴C-methoprene. The results showed that plasma radioactivity peaked at approximately 6 hours and declined slowly with a half life of about 48 hours during the second to fifth day of dosing. The total amount of radioactivity in the plasma at 6 hours was about 1.63% of the administered dose.

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The tissue distribution study showed the distribution of radioactivity in rats at 1, 3, 6, 12, 24, 72, 120 and 288 hours following oral dosing with 25 mg/kg of radiolabelled methoprene. In this portion of the study, the highest concentrations of radioactivity were initially observed in the liver, kidney, lungs (peaking at 6 hours) and fat (peaking at 12 hours). After 5 days most of the residual radioactivity was in the fat (8.5% of dose) and muscle (2.2% of dose). Whole body autoradiographs showed extensive distribution of radioactivity. High levels being observed after 6 hours in the stomach, liver, small intestines, brown fat, and significant levels were present in the kidneys, salivary and lachrymal glands, brain, thyroid, thymus, spleen, lungs, adrenals, myocardium and bone marrow. Of special interest was the high levels of radioactivity observed in the adrenal cortex at 5 and 12 days. The authors suggested that the high levels of radioactivity observed here may indicate the incorporation of methoprene metabolites into pathways of steroid biosynthesis.

In the above tests, unchanged methoprene was observed only in the feces and was present in small amounts. 12 radiolabelled metabolites were identified in the urine. Most of these metabolites were considered to be carboxylic acids since they were converted to less polar compounds on treatment with diazomethane. In the bile, the major portion of the radioactivity was associated with a very polar material that was unaffected by enzyme treatment. These data confirm the extensive and relatively rapid metabolism of methoprene in the rat.

The metabolism of methoprene was investigated in mice (Zoecon Corporation, 1972, MRID: 00010425 and Cline et.al., 1972, MRID: 00010424). In these studies 10 Swiss mice, 8 males and 2 females at midgestation, were given a single dose of 7.7 mC/g body weight of tritium labelled methoprene (labelled at the C-10 position) intragastrically in 3% ethanol. The radioactivity in the urine, feces and whole body was monitored for up to 4 days. The results showed that 68% of the radioactivity was eliminated in the urine and 14% in the feces by 4 days. A glucuronide conjugate of ZR-724 (11-hydroxy-3,7-11-trimethyl-dodeca-2,4-dienic acid) was a major urinary metabolite. In the feces, unchanged methoprene and chromatograph metabolites, similar to some observed in urine samples were detected. However, fecal metabolites were not qualitatively identified.

Whole body autoradiographs indicated transient radiolabel in the stomach, liver, small intestines and large intestines up to 24 hours following dosing. By 48 hours there was negligible retention of the radiolabel in the body. Placental transfer of the radioactivity was not detected in the pregnant mice.

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In a study that was designed to give a preliminary quantification and identification of methoprene and its metabolites in urine, feces, exhaled air, blood and tissues, one guinea pig was given a single oral dose of 49 mg/kg of ^{14}C -labelled methoprene (95-98% A.I.) (Chamberlain et.al., 1973, MRID: 00010379). The distribution and elimination of the radioactivity was monitored for 24 hours following dosing. The results showed that 24.3% of the radiolabel was recovered in the urine, 9.1% in the feces and 17.2% in the exhaled air by 24 hours. Blood contained 18.18 ug ^{14}C -equivalents per gram weight while muscle contained 14.3 ug equivalents per gram dried (or 3.31 ug per gram wet) and fat contained 10.95 ug equivalents per gram of tissue.

Chromatographic analyses indicated that approximately 79% of the fecal radioactivity was unchanged methoprene. In the urine a large proportion of the recovered radiolabel was glucuronic acid conjugates of ZR-724 (11-hydroxy-3,7,11-trimethyl-dodeca-2,4-dienoic acid), ZR-725 (11-methoxy-3,7,11-trimethyl-dodeca-2,4-dienoic acid) and ZR-669 (isopropyl 11, hydroxy-3,7,11-trimethyl-dodeca-2,4-dienoate); the remaining metabolites were mostly unidentified polar compounds. No intact methoprene was detected in the urine.

Data were available to demonstrate the exhaustive biodegradation of methoprene in the steer (Zoecon Corporation, 1973, MRID: 00011491, Staiger et.al., 1973, MRID: 00010879 and Chamberlain et.al., 1973, MRID: 00010380, Quistad et.al., 1975, MRID: 05008609). In a study, the radioactivity in urine, feces, blood, tissues and samples of expired air was monitored for up to 2 weeks in a steer given a single oral dose of 2 g ^{14}C -methoprene (96.9% A.I.). The total recovery of radioactivity was 78% of the administered dose. Urine contained 21.6% of the recovered radiolabel (with peak levels observed at 36 hours) and feces accounted for 38.8% of it (peak levels were observed at 48 hours). Samples of expired CO_2 accounted for 2.7% of the recovered radiolabel while blood and tissues accounted for 13.5% of it. Blood levels of radioactivity peaked at 72 hours and remained high until sacrifice at 2 weeks. Tissue radioactivity was highest in the gall bladder followed by the liver, lung, kidney, spleen and heart.

In the urine up to 14 different radiolabelled metabolites were identified. Most of these metabolites were more polar than methoprene or its primary metabolites (i.e. ZR-669, ZR-724 or ZR-725). Fecal extracts contained up to 7 radioactive metabolites of which the parent methoprene was the principal component (5-50% depending on sampling time). At 72 hours the following radioactive components were identified in the feces: 32% methoprene, 12% ZR-669, 4% ZR-725, 4% ZR-724 and less than 1% as ZR-1995; the remaining radioactivity was unidentified polar metabolites.

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Analysis of the radioactive distribution in selected tissues showed no residues of methoprene or its known metabolites. However, significant amounts of label were identified in the form of cholesterol and in the case of bile in cholic and deoxycholic acids. Chemical degradation of labelled cholesterol and cholic acid showed ^{14}C incorporation into the steroid nucleus corresponding to the biosynthetic incorporation of ^{14}C -2-acetate.

In the above study, 22% of the administered radiolabelled was unaccounted for experimentally. However, the authors attributed the loss to the sampling techniques used to collect expired air. This explanation is consistent with the observations in rats and guinea pig that indicated significant recovery of radioactivity in expired CO_2 .

The fate of radiolabelled methoprene (5- ^{14}C -methoprene, 95% A.I.) in urine, feces, expired air, blood, tissues and milk was investigated in a pregnant lactating jersey cow for up to 7 days following the oral administration of 207.6 mg of 5- ^{14}C -methoprene. (Zoecon Corporation, 1974, MRID: 00010681, Quistad et.al., 1974, MRID: 00010625, and Chamberlian et.al., 1974, MRID: 00010683). In this study, the total radioactivity recovered during 7 days accounted for 94% of the applied dose. The following distribution was observed: 19.7% in the urine (peak recovery at 30 hours), 30.3% in feces (peak recovery at 50 hours), an estimated 16.4% in expired CO_2 (peak recovery at 24 hours), 7.6% in milk and 20% in tissues. In the tissues, the highest concentrations of radiolabel were detected in the gall bladder, liver, kidney, ovaries and lungs. Recovery of radiolabel from the fetus accounted for approximately 1% of the original dose. Approximately 0.8% of the recovered radiolabel in the milk was unchanged methoprene. Most of the radioactivity in the milk was incorporated into lipids, lactose and proteins. Radiolabelled acetate was isolated from a 48 hour blood sample and provided good evidence for label recycling and incorporation of methoprene metabolites into natural body constituents.

These data are considered adequate to fulfill methoprene metabolism data requirements. The findings indicate rapid and extensive biodegradation of methoprene and its metabolites in mammalian species. Evidence was presented to show that methoprene metabolites are incorporated into natural body constituents.

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Domestic Animals

Chickens

White Leghorn chicks were fed diets containing 215, 464, 1000, 2150 or 4640 ppm technical methoprene (86.9% A.I.) for 5 days. (Fink, 1973, MRID: 00010577). No mortality or clinical signs of toxicity were observed during an 8 day observation period. The data indicate that repeated high doses of methoprene are well tolerated in chicks. Based on food consumption and body weight data, an acute oral LD₅₀ in chicks is estimated as greater than 1 g/kg.

In another study (Halloran, 1975, MRID: 00010632), 10 or 30 ppm methoprene (% A.I. unspecified) in the diet of laying hens for 6 weeks did not cause mortality or molting. In addition, methoprene at these concentrations had no effect on egg production, feed intake, feed conversion, egg weight, shell thickness, albumin height, Haugh Units, yolk color or hen weight.

Fink, J. 1973. Paper presented at the 1973 Annual Meeting of the Society of Environmental Toxicologists and Chemists, San Francisco, California. Unpublished paper received February 1974. Under 1095-0001 prepared in cooperation with Wallace Farms, Inc., submitted to Wallace Farms, Palo Alto, Calif. COA 111-000-000-0001-0001-0001.

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Human Exposure

The Pesticide Information Monitoring System (PIMS) reported one incident involving accidental human exposure to methoprene, alone. The monitoring system contains information on reported pesticide exposures to humans from 1966 to July, 1979. In this case, a 2 1/2 year old boy remained asymptomatic after methoprene from a pressurized container got into his mouth. The incident occurred in the home.

Zoecon Corporation (1973, MRID: 00010793) reported 40 incidents involving accidental methoprene exposure to male chemical workers. The incidents involved 26 exposures to technical methoprene and 14 exposures to a formulated product (10% E.C.). Exposure to the technical product was through dermal contact in 19 out of 26 cases and involved vapor exposure in 7 instances. Exposure to the 10% E.C. product was via dermal contact in 12 out of 14 cases and via the vapors in 2 instances. In all cases, no overt signs of toxicity were observed. Treatment in the majority of incidents consisted of washing the chemical off with soap and water. No medical treatment was indicated.

In addition, the Zoecon report cited two other incidents involving accidental exposure to methoprene. In the most serious incident, a male plant operator was coated with methoprene on the forehead, neck, forearms and hand following an explosion. After washing with soap and water the victim did not experience any dermal or clinical signs of toxicity. In the other incident (under undescribed circumstances), no ill effects resulted from the extended dermal and inhalation exposure to technical methoprene in a male worker.

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Methoprene

Disciplinary Review

Toxicology Profile
Toxicity Hazard Assessment
Generic Data Gaps

TOXICOLOGY PROFILE

Technical Methoprene

Sufficient data were available to adequately assess the acute toxicity of technical methoprene. The high acute oral LD₅₀ in rats, greater than 10 g/kg (Hallesy et.al., 1972, MRID: 00024607), the relatively high acute oral LD₅₀ in dogs, greater than 5 g/kg but less than 10 g/kg (Hallesy et.al., 1972, MRID: 00024609), the relatively high acute dermal LD₅₀ in rabbits, greater than 2 g/kg (with a 65.9% E.C.) (Hepler et.al., 1972, MRID: 00010914) and the high acute inhalation LC₅₀ in rats, greater than 20 mg/L (Olson and Willigan, 1972, MRID:) indicate a low acute toxicity potential in humans.

Sufficient data were available to assess the primary eye and primary dermal irritation potentials of technical methoprene. In an eye irritation study (Hill and Hallesy, 1972, MRID: 00024614) 0.1 ml of technical methoprene did not cause eye irritation or corneal opacity in rabbit eyes. In addition, when rabbits were given 24 hour dermal exposure to 0.5 ml technical methoprene, on shaved, abraded and unabraded skin, (Hallesy and Hill, 1972, MRID: 00024615) no dermal irritation was observed for up to 72 hours. These data indicate that technical methoprene is not a primary eye or dermal irritant. Thus, it is expected to have a low potential for eye and dermal irritation in humans.

There were no studies on the skin sensitization potential of technical methoprene. However, based on the acute data described above, information on the acute intraperitoneal toxicity of methoprene in rats (LD₅₀ = 4.8 g/kg) (Jorgenson and Sasmore, 1972, MRID: 00024613) and an assessment of the chemical structure of methoprene, dermal sensitization is not anticipated with this chemical. Therefore, this data requirement can be waived.

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Adequate data were available to assess the subchronic oral toxicity of methoprene in rats. (Jorgenson and Sasmore, 1972, MRID: 00024612). In a 90-day feeding study, the NEL for systemic toxicity was determined to be 500 ppm. The lowest effect level (LEL) was 1000 ppm. In dogs, a 90-day NEL for systemic toxicity was established as 500 ppm and the LEL was 5000 ppm (Jorgenson and Sasmore, 1972, MRID: 00024612). Taking into consideration the feed conversion factor these data indicate that the dog is more sensitive (NEL = 12.5 mg/kg) to methoprene toxicity than the rat (NEL = 25 mg/kg). Thus, an additional feeding study, of a longer duration, is needed with the dog.

Insufficient data were available to evaluate the subchronic dermal toxicity of methoprene. A 21-day dermal toxicity study in rabbits was conducted at Industrial Biotest Laboratories, 1972, however, the toxicological evaluation of this study is pending receipt of the results from the audit validation program. At present this testing requirement constitutes a data gap.

Supplementary data were available to assess the subchronic inhalation toxicity of technical methoprene. In a 21-day inhalation study in rats (Olson and Willigan, 1972, MRID:), the NEL was determined to be 20 mg/L (HDT - highest dose tested). Additional testing is not required, since pesticidal use is not likely to result in repeated human inhalation exposure at a concentration likely to be toxic, as determined from this data.

Sufficient data were available to show that methoprene is not teratogenic or fetotoxic in rabbits at doses as high as 200 mg/kg given on gestation days 6 through 15 (Nomura Research Institute, 1975, MRID:). At 2000 mg/kg (LEL - lowest effect level) maternal toxicity and embryolethality were observed. In a supplementary study in mice (Nomura Research Institute, 1975, MRID:), no teratology, fetotoxicity or maternal toxicity were observed in mice given 0, 50, 200 or 600 mg/kg/day methoprene on days 7 through 14 of gestation. Because of some deficiencies in reporting methodology and results, the registrant has been asked to submit additional data for this study. An assessment of the adequacy of this study to fulfill Guideline Teratology Testing Requirements, is pending receipt of additional data from the registrant.

Teratology studies in rats and rabbits, using technical methoprene, were conducted at Industrial Biotest Laboratories, 1972. The toxicological evaluation of these studies is pending receipt of the results from the audit validation program.

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Sufficient data were available to assess the reproductive toxicity of methoprene in rats. In a three generation reproduction study (Killeen and Rapp, 1974, MRID: 00010571), the NEL was determined to be 2500 ppm (HDT). Further testing in this discipline is not required.

Adequate data were available to assess the chronic feeding toxicity and oncogenic potential of methoprene. In a 2-year feeding study with rats (Wazeter and Goldenthal, 1976, MRID: 00010739), the NEL for systemic toxicity and oncogenicity was determined to be 5000 ppm (HDT). In an 18-month oncogenicity study with mice (Wazeter and Goldenthal, 1975, MRID: 00010600) the NEL for oncogenicity was determined to be 2500 ppm (HDT) while the NEL for systemic toxicity was established as 250 ppm (1000 ppm was the LEL).

The metabolism of methoprene was adequately investigated in a series of studies with the rat, mouse, guinea pig, steer and cow (MRID: 00010866, 05007755, 00010425, 00010424, 00010379, 00011491, 0001879, 00010380, 05008609, 00010681, 00010626 and 00010683). These studies indicated rapid and extensive biodegradation of methoprene and its metabolites in mammalian species. In addition, evidence was presented to show that methoprene metabolites are incorporated into natural body constituents.

A bacterial assay (Hsia et al., 1979, MRID: 05018270) and a dominant lethal study (Johnston, 1973, MRID: 00010545) presented evidence indicating that methoprene is not mutagenic. Although these studies are not adequate to fulfill mutagenicity data requirements, they do suggest a lack of genetic toxicity with methoprene. Since a mutagenic effect is not anticipated, this data requirement can be waived at this time. However, the Agency reserves the right to ask for additional mutagenicity testing if a need is indicated in the future.

Data to assess the toxicity of methoprene in domestic animals was also available. In an 8 day feeding study in chicks (Fink, 1973, MRID: 0001577), a NEL of 4640 ppm (HDT) was established. Based on food consumption and body weight data an acute oral LD₅₀ for methoprene in chicks was estimated to be greater than 1 g/kg. In a 6 week feeding study in laying hens (Holloran, 1975, MRID: 00010362), 30 ppm (HDT) was determined to be the NEL. Methoprene at this concentration had no effect on egg production, feed intake, feed consumption, egg weight, shell thickness, albumin height, Haugh Units, yolk color or hen weight.

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Manufacturing Use (M.U.) Methoprene

Insufficient data were available to assess the acute toxicity of the M.U. formulations containing 10-80% methoprene.

Based on an evaluation of the inert ingredients, acute oral toxicity, acute dermal toxicity and acute inhalation toxicity testing is required with the existing M.U. product containing 15% methoprene.

No data were available to assess the primary eye irritation potential of the M.U. formulated products of methoprene. Based on an evaluation of the inert ingredients, eye irritation testing with each of these products is required.

Insufficient data were available to assess the primary dermal irritation and dermal sensitization potentials of the M.U. formulations of methoprene. Based on an evaluation of the inert ingredients, these tests are required with the existing M.U. product containing 15% methoprene.

End Use Products

Emulsifiable Concentrates (E.C.)

Adequate data were available to assess the acute oral and dermal toxicity of E.C. formulations containing 5-65.9% methoprene. The acute oral LD₅₀ in rats, was greater than 5 g/kg for a 65.9% E.C. product and greater than 10 g/kg for a 10% E.C. product (Hepler et.al., 1979, MRID: 00010913 and Hallesy et.al., 1972, MRID: 00024608). The acute dermal LD₅₀ in rabbits, was greater than 2 g/kg for a 65.9% E.C. product and greater than 9 g/kg for a 10% E.C. product (Hepler et.al., 1979, MRID: 00010914 and Olson, 1972, MRID: 00024618).

These data indicate a low acute toxicity potential for the E.C. formulations of methoprene in humans.

Although no studies were available on the acute inhalation toxicity of the E.C. formulations, based on an evaluation of the inert ingredients and the available acute toxicity data that indicates a low toxicity potential for these products, this data requirement can be waived.

Sufficient data were available to show that the E.C. formulations of methoprene are not primary dermal irritants. When rabbits were given 24 hour dermal exposure, on shaved, abraded and intact skin, to 0.5 ml of a 65.9% E.C. product or a 10% E.C. product of methoprene, the primary dermal irritation score was "0" out of a possible 8 score (Hepler et.al., 1979, MRID: 00010915 and Hallesy and Hill, 1972, MRID:). Based on the Confidential Statement of Formulation (CSF) the 5% E.C. product is not anticipated to be a primary dermal irritant, additional testing is not needed.

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The eye irritation potential of E.C. formulations of methoprene can be adequately assessed for the products containing 65.9% and 10% methoprene. 0.1 ml of the 65.9% E.C. product caused slight conjunctival irritation in washed and unwashed rabbit eyes for up to 72 hours following instillation. (Hepler et.al., 1979, MRID: 00010915). In addition, slight conjunctival irritation was observed at 1 hour following instillation of 0.1 ml of the 10% E.C. product in rabbit eyes. This condition had cleared by 24 hours in both washed and unwashed eyes (Hallesy and Hill, 1972, MRID:). These data indicate that the 65.9% and 10% E.C. formulations of methoprene are not primary eye irritants. However, in humans transient eye irritation could result from the accidental spillage of these products into the eyes.

No data were available to assess the primary eye irritation potential of the 5% E.C. product. Based on an evaluation of the inert ingredients, this test is needed.

No studies were available on the skin sensitization potential of the E.C. products of methoprene. However, based on the inert ingredients and the available acute data, dermal sensitization is not anticipated with these products. Therefore, testing in this discipline can be waived.

Granular (G) and Pelleted/Tabeleted (P/T)

No studies were available on the acute oral, acute dermal or acute inhalation toxicities of the G or P/T formulations containing 0.02 to 7.9% methoprene. Since the CSF's do not indicate an anticipated change in the acute toxicities of these products, due to their inert ingredients, testing of the technical chemical is sufficient. Therefore, additional testing in these disciplines is not needed.

No studies were available on the primary eye and dermal irritation and dermal sensitization potentials of the G and P/T formulations of methoprene. Based on the CSF's and the available acute data for methoprene, dermal irritation and dermal sensitization are not anticipated with these products, therefore these tests are not needed. However, eye irritation could result from accidental eye exposure to these products, therefore one eye irritation test is required with a G product. This test will satisfy eye irritation testing requirements for the existing G and P/T products.

Pressurized Liquids (P.R.L.)

No data were available to assess the acute oral, acute dermal and acute inhalation toxicity of the P.R.L. formulation containing 0.15% methoprene. Based on an evaluation of the inert ingredients, testing of the M.U. product containing 15% methoprene should be sufficient to fulfill these data requirements. Therefore, separate acute toxicity testing with the P.R.L. product is not needed.

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No data were available to assess the primary eye irritation potential of the P.R.L. formulation of methoprene. Since this product contains a propellant, separate eye irritation testing is needed.

No data were available to assess the dermal irritation and dermal sensitization potential of the P.R.L. liquid formulation of methoprene. Based on an evaluation on the inert ingredients, testing of the M.U. product containing 15% methoprene should be sufficient to fulfill these data requirements. Thus, separate dermal irritation and dermal sensitization testing are not needed with this product.

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TOXICITY HAZARD ASSESSMENT

Technical Methoprene

The acute toxicity of methoprene is low since the LD₅₀ values for acute oral, dermal and inhalation toxicity are high. There are no chronic, oncogenic, mutagenic, teratogenic or reproductive hazards associated with the chemical as indicated by experimental data. Methoprene is not a primary eye or dermal irritant and it is not anticipated to cause dermal sensitization.

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XXXXXXXX Product-Specific Data Requirements for *chemical*

Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliography Citation	Must Additional Data be Submitted under FIFRA 3(e)(2) (B)? If so, within allowed for submission from established date of standard
163.01-1	Acute Oral Toxicity	yes/no	Technical	yes/no	MSID: 00024627	yes/no
163.01-2	Acute Dermal Toxicity	yes/no	"	yes/no	MSID: 00010914	yes/no
163.01-3	Acute Inhalation Toxicity	yes/no	"	yes/no	MSID: _____	yes/no
163.01-4	Primary Eye Irritation	yes/no	"	yes/no	MSID: 00024614	yes/no
163.01-5	Primary Dermal Irritation	yes/no	"	yes/no	MSID: 0024615	yes/no
163.01-6	Dermal Sensitization	yes/no	"	yes/no		yes/no

- 1) Based on the available acute data, the test results are not sufficient to determine if dermal sensitization is not anticipated; therefore, this data requirement can be waived.
- 2) Data available for an 45.9% E.C. is considered sufficient to satisfy the data requirement.

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XXXXXXX Toxicology (see Chapter VI)
 XXXXXXXX Product-Specific Data Requirements for ~~Manufacturing~~ *the technical chemical*

Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2) (B)? If so, months allowed for submission from published date of standard
163.01-7	Acute Delayed Neurotoxicity	yes/no		yes/no		yes/no
163.02-1	Subchronic Oral Toxicity	yes/	-	yes/ MPTD: 00024612		yes/ 30
163.02-2	Subchronic 21-Day Dermal Toxicity	yes/	-	yes/no 34		yes/ 30

36] A 21-Day dermal toxicity study was conducted in I.T., 1972. The toxicology evaluation of this test is pending receipt of the results from the I.T. and/or program. If the study is determined to be valid, additional testing will not be needed.

39] A 90 day oral and dermal toxicity study were submitted in partial fulfillment of the subchronic oral toxicity data requirement. However, further data longer duration is needed in dermal.

XXXXXXX Toxicology (see Chapter VI)
 XXXXXXXX Product-Specific Data Requirements for ~~Manufacturing~~ *the technical chemical*

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Toxicology (see Chapter VI)
 XXXXXXXX Generic Data Requirements for Manufacturing Use Products for the Technical Class

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2) (B)? If so, months allowed for submission from published date of standard
165.833-3	Subchronic 90-day Dermal Toxicity	yes/no		yes/no		yes/no
165.833-4	Subchronic Inhalation Toxicity	yes/no		yes/no		yes/no
165.833-1	Chronic Oral Feeding Toxicity	yes/no	Technical	yes/no	MRID: 00010739	yes/no
165.833-2	Oral Oncogenicity	yes/no	U	yes/no	MRID: 00010739 00010666	yes/no
165.833-3	Oral Teratogenicity	yes/no	U	yes/no	MRID: _____	yes/no 41
165.833-4	Oral Reproduction	yes/no	U	yes/no	MRID: 00010571	yes/no
165.833-2 through -4	Mutagenicity	yes/no	U	yes/no	MRAD: 05018270 00010545	yes/no

4) Adequate data is available to conduct the teratogenic potential of methoprene in rabbits. Additional information concerning a test for teratogenicity of methoprene is not needed. The value has been taken from the test results.

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Toxicology (see Chapter VI)
XXXXXXXXX Product-Specific Data Requirements for Manufacturing-Use Products

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2) (B)? If so, months allowed for submission from published date of standard
163.01-1	Acute Oral Toxicity	yes/	15% A.I.	yes/no	-	yes/no
163.01-2	Acute Dermal Toxicity	yes/	15% A.I.	yes/no	-	yes/no
163.01-3	Acute Inhalation Toxicity	yes/	15% A.I.	yes/no	-	yes/no
163.01-4	Primary Eye Irritation	yes/	10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100% A.I.	yes/no	-	yes/no
163.01-5	Primary Dermal Irritation	yes/	15% A.I.	yes/no	-	yes/no
163.01-6	Dermal Sensitization	yes/	15% A.I.	yes/no	-	yes/no

163.01-1, 163.01-2, 163.01-3, 163.01-4, 163.01-5, 163.01-6

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Emulsifiable Concentrates (E.C.)

Toxicology (see Chapter VI)
XXXXXXXXXX Product-Specific Data Requirements for End-Use Products

Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2) (B)? If no, months allowed for submission from published date of standard
1. Ready-to-Use						
163.81-1	Acute Oral Toxicity	yes/	5-65.9% A.I.	yes/ MRID: 00010913 and 00024602		yes/no
163.81-2	Acute Dermal Toxicity	yes/	5-65.9% P.I.	yes/ MRID: 00010914 and 00024618		yes/no
163.81-3	Acute Inhalation Toxicity	yes/	5-65.9% P.I.	yes/ MRID: _____		yes/no
163.81-4	Primary Eye Irritation	yes/	10-65.9% P.I.	yes/ MRID: 00010945		yes/ 5/
163.81-5	Primary Dermal Irritation	yes/	5-65.9% P.I.	yes/ MRID: 00010915		yes/no
163.81-6	Dermal Sensitization	yes/	5-65.9% A.I.	yes/ 61		yes/no

5/ Testing with the E.C. product is needed

6/ Based on an evaluation of the inert ingredients and the available toxicity data, dermal sensitization and sublethal oral toxicity studies, the data for the E.C. product can be used.

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Granular and Pelleted Tableted

Toxicology (see Chapter VI)
XXXXXXXXXX Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2) (H)? If so, months allowed for submission from published date of standard
2. Pressurized Liquid						
163.01-1	Acute Oral Toxicity	yes/ <input checked="" type="checkbox"/>	0.02 - 7.9% AI	yes/ <input checked="" type="checkbox"/> MRID: 00024607		yes/no
163.01-2	Acute Dermal Toxicity	yes/ <input checked="" type="checkbox"/>	↓	yes/ <input checked="" type="checkbox"/> MRID: 00010444		yes/no
163.01-3	Acute Inhalation Toxicity	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/> MRID: _____		yes/no
163.01-4	Primary Eye Irritation	yes/ <input checked="" type="checkbox"/>		yes/no	-	yes/ <input checked="" type="checkbox"/> 6
163.01-5	Primary Dermal Irritation	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/> MRID: 00024615		yes/no
163.01-6	Dermal Sensitization	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/> 8	-	yes/no

7) Testing with one granular formulated product is needed. The results of this test will fulfill testing requirements for the pelleted tableted formulations also.

8) Based on the available data for technical methoprene, dermal sensitization is not necessary with these pellets therefore the data requirement may be waived.

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Pressurized Liquid

Toxicology (see Chapter VI)
XXXXXXXXXX Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2) (B)? If so, months allowed for submission from published date of standard
<u>3. Impregnated Materials</u>						
163.01-1	Acute Oral Toxicity	yes/ <input checked="" type="checkbox"/>	0.15% AI ↓	yes/ <input checked="" type="checkbox"/>	-	yes/ <input checked="" type="checkbox"/> 91
163.01-2	Acute Dermal Toxicity	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/>	-	yes/ <input checked="" type="checkbox"/> 91
163.01-3	Acute Inhalation Toxicity	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/>	-	yes/ <input checked="" type="checkbox"/> 91
163.01-4	Primary Eye Irritation	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/>	-	yes/ <input checked="" type="checkbox"/>
163.01-5	Primary Dermal Irritation	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/>	-	yes/ <input checked="" type="checkbox"/> 91
163.01-6	Dermal Sensitization	yes/ <input checked="" type="checkbox"/>		yes/ <input checked="" type="checkbox"/>	-	yes/ <input checked="" type="checkbox"/> 91

91 Testing of the 15% M.V. product will be sufficient to fulfill this data requirement.

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BEST DOCUMENT AVAILABLE

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